ESTIMATION OF THE RISK OF STOCHASTIC (CANCER) EFFECTS OF OCCUPATIONAL RADIATION EXPOSURE
Project 2.2

Proposal presented to the Joint Coordinating Committee on Radiation Effects Research

Principal Investigators:

For Russia: Nina A. Koshurnikova
Branch 1 of the Biophysics Institute, Ozersk

For the United States: Ethel Gilbert
National Cancer Institute, Bethesda, MD

Participating Investigators

For Russia:
M.G. Bolotnikova
V.V. Kreslov
P.V. Okatenko
M.E. Sokolnikov
N.S. Shilnikova
L.G. Filippova

V.F. Khokhryakov
K.G. Suslova,
S.A. Romanov,
T.I. Kudryavtzeva
I.A. Orlova
Branch 1 of the Biophysics Institute, Ozersk

E.K. Vasilenko
Mayak Production Association

For the United States:
Elaine Ron
National Cancer Institute, Bethesda, MD

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Abstract

A direct quantitative assessment of risks from protracted radiation exposure is needed to evaluate the appropriateness of current radiation protection standards. Epidemiologic studies of workers at nuclear plants in Russia, the United States, and other countries have the potential to become one of the most important sources of data for this assessment. Workers at the Mayak facility in the Chelyabinsk region of Russia provide information that is not available from other studies, including information on risks from large protracted exposures, risks in female workers, and risks from internal plutonium exposure. The objective of the long-term project 2.2 is to obtain cancer risk estimates based on protracted occupational radiation exposure, both from external gamma-radiation and from internal alpha-radiation from plutonium. Work indicated in this proposal is addressed at meeting this objective and includes improvement of the computer database; updating vital status data; development of an adequate control group; the conduct of dose-response analyses addressing risks of lung, bone and liver tumors resulting from plutonium exposure; and comparison of results with those based on workers in the United States. This work will be closely coordinated with efforts addressed at understanding and improving historical dosimetry, and will make use of the best available estimates of both external and internal doses.

Specific Aims

The objective of this long-term project is to obtain cancer risk estimates based on protracted occupational radiation exposure, both from external gamma-radiation and from internal alpha-radiation from plutonium. To meet this objective, work in the areas indicated below is needed.

<u>Task 1: Improvement of the computer database.</u> Data on where workers were employed (reactor, radio-chemical, and plutonium production) during any given time period will be improved. In addition, a comprehensive set of logical checks will be developed, documented, and performed; and any identified discrepancies will be resolved.

<u>Task 2: Update of vital status data.</u> Currently data on vital status and cause of death is available through the end of 1994. This work will update this information to extend to the end of 1996.

<u>Task 3: Development of an adequate control group.</u> Most monitored workers employed in the main Mayak facilities received substantial doses in the early period of Mayak operations. In addition, national statistics are unlikely to provide an appropriate basis for comparison, and, furthermore, are not available for all causes of death and time periods of interest. Thus, it is proposed that a control group be developed from unmonitored workers and from workers at the auxiliary plants of Mayak.

<u>Task 4: Conduct dose-response analyses to evaluate risks of lung, liver and bone cancer resulting from plutonium exposure.</u> Under the project currently being funded by the NCI, dose-response analyses based on currently available data on external doses are being conducted. Project 2.2 will expand these analyses to include analyses of lung, bone, and liver cancer (sites

where internal exposure to plutonium contributes substantially to dose) based on estimated doses from both external and internal sources. These analyses will make use of the best available dosimetry data.

Task 5: Comparison of the results of analyses conducted under 2.4 with results from studies in the United States. Data on the effects of plutonium in U.S. workers are limited because of the generally small exposures and small sample sizes. Nevertheless, results from the Mayak cohort will be compared with available published results from U.S. studies.

Background and Significance

The most reliable radiation risk estimates for carcinogenic effects have been obtained from the epidemiologic studies of the Japanese A-bomb survivors. Recent results show increased risks for most cancer sites. Additional information is available from studies of persons who received radiation therapy. Despite the large amount of data accumulated, questions remain regarding the appropriateness of using radiation risk estimates obtained from a single exposure at high dose rates (as in the A-bomb survivor studies) for other practically important exposure scenarios, including protracted exposures and exposure from internally deposited radionuclides. The assessment of cancer risk due to protracted exposure is important because most exposures of interest for risk assessment (including occupational exposure) are protracted. Irradiation from internal emitters remains relevant because of the need to conduct work to eliminate accumulated nuclear weapons and to reprocess spent fuel elements.

Several studies of workers in the United States, United Kingdom, and Canada have been carried out (Gilbert 1995), and combined analyses at both the national (Gilbert et al. 1993; Carpenter et al. 1995) and international level (Cardis et al. 1995) have been conducted. The mean cumulative dose for the international study was 46 mSv. The distribution of doses was highly skewed; nearly 60% of the workers had cumulative doses below 10 mSv, and less than 2% had doses exceeding 400 mSv.

An issue of interest for this proposal is the choice of a suitable control group. The worker studies noted above included comparisons with death rates based on national statistics. Such comparisons are difficult to interpret because of the generally lower death rates that are experienced by employed persons as compared with the general population. This "healthy worker effect" specifically affects death rates from cancer. For example, standardized mortality ratios for all cancers were significantly reduced in 9 out of 10 nuclear worker studies in the U.S., U.K. and Canada (Gilbert 1995). The healthy worker effect may be especially pronounced in Mayak workers because of strict medical screening.

Because of difficulties related to the healthy worker effect, the worker studies discussed above have relied primarily on internal comparisons by level of radiation dose. This approach has worked well because these studies have included large numbers of workers with little or no occupational exposure. In these studies, analyses that treat exposure as a quantitative variable and that evaluate the increase in risk with increasing exposure have been emphasized. In conducting such analyses, it has not been necessary to designate a specific group as the control, but the large number of workers with very low doses has served to "anchor" the dose-response function and has led to more stable estimates of risk than would have been possible without a large group of relatively unexposed workers. Analyses of data on Japanese A-bomb survivors have followed the same principles with emphasis on internal dose-response analyses.

Studies of workers in other countries provide a direct evaluation of risks from protracted exposure to external radiation at relatively low doses, and the national and international combined analyses have provided reassurance that extrapolation from high dose studies has not seriously underestimated risks. However, the relatively low external doses received by most workers limits power for studying the possible modifying effects of exposure protraction, and these studies have shown consistency both with no risk and risks that are somewhat larger than those obtained from high dose studies. Also, because most of the exposure was to males, almost no information is available on radiation risks in female workers.

Studies of workers exposed to plutonium in the U.S. have been reviewed by Voelz (1991), and include workers at Los Alamos National Laboratory, Los Alamos Zia Corporation, Mound Laboratory, and Rocky Flats Nuclear Weapons plant. Small numbers of workers at the Hanford, Oak Ridge, and Savannah River sites have also been exposed, but the effects of this exposure have been examined only for the Hanford cohort. Voelz indicates that only about 50 persons had body burdens exceeding 1,480 Bq, the lifetime maximum permissible body burden guideline used during most of the period of follow-up. Analyses of these data have been based primarily on estimated body burdens rather than on organ doses. Clearly, these studies can provide only very limited information on plutonium-related health effects.

The Mayak nuclear facility, located in the Chelyabinsk region of the Russian Federation, began operations in 1948, and is managed by the Mayak Production Association (PA). The facility has nuclear reactors, a radiochemical plant, and a plutonium production facility. During the first decade of Mayak's operation, workers at the plants were exposed to doses of external gamma radiation that were substantially higher than current occupational dose limits, and were also exposed to inhaled plutonium at levels much higher than those considered permissible today. Film badge dosimetry data for the Mayak cohort are available at the Radiation Safety Service of the Mayak PA. Data on levels of plutonium content in excreta, accumulated since 1970 from periodic biophysical examinations of workers at the facility, are available at Branch 1 of the Biophysics Institute (FIB-1), and have been used to develop estimates of dose to the lung and other organs for about 30% of workers with a high probability of exposure. It is noted that a proposal to provide a data base of improved external and internal dose estimates for both projects 2.2 and 2.3 is being submitted; this work would be conducted by investigators at Mayak and FIB-1.

Study of the Mayak cohort can fill important gaps in our knowledge of radiation risks by providing information on protracted external exposure at high doses, on occupational exposure in females, and on exposure from internally deposited plutonium. Together, studies of nuclear plant workers in the Russian Federation and the United States (and other countries) offer the possibility of obtaining radiation risk estimates based on a wide range of individually measured doses of external gamma- and internal alpha-irradiation. Difficulties related to limited sample size and statistical power can be at least partially addressed by long-term follow-up and, in some cases, by combining data from several cohorts.

Preliminary Studies

The final report for the first year of work on project 2.2 provides a detailed description of the development of the Mayak Worker Registry. Appendices to this report describe the content of the registry, determination of vital status, validation of radiation doses, and identification of a comparison group. This final report is attached as an appendix to this proposal. A summary of work that is especially relevant for this proposal is given below.

About ten years ago, Dr. Koshurnikova and colleagues at FIB-1 began to create the Mayak Worker Registry. Information was extracted from several sources and much of it has been computerized. The computerized registry
now contains occupational histories, annual and cumulative gamma doses, plutonium body burdens and internal doses to the main organs of plutonium deposition (lung, liver and bone), date and place of birth, current and past names, current place of residence, vital status, date and causes of death. In some cases, data are also available on chronic diseases, smoking and drinking habits, and contact with harmful occupation agents before employment at Mayak PA.

Vital status has been determined primarily through the use of the Ozyorsk address bureau, and, for non-residents, by making inquiries at address bureaus in places where subjects have subsequently resided. Data on date and cause of death are obtained from several sources depending on where the death occurred. Vital status is known for about 89% of all workers, but this percentage is 85% for persons who began working between 1948-53.

The Mayak Worker Registry currently includes about 19,000 persons. About 14,000 of these workers have known vital status and film badge dosimetry data, and more than 4,000 have measured plutonium body burdens. About 4,000 persons have died, 1,000 of them from cancer. The average external gamma-dose for workers included in the registry is 0.88 Gy: 0.66 Gy for the atomic reactor workers, 1.22 Gy for the radiochemical plant workers, and 0.44 Gy for the plutonium production plant workers. These radiation doses decreased significantly with time with average external doses of 1.57, 0.57, 0.27 and 0.15 Gy for workers hired in the respective time periods 1948-53, 1954-58, 1959-63, and 1964-72. The average value of the equivalent dose to the lung for all workers with measured plutonium body burden is 7.06 Sv: 4.09 Sv for the radiochemical plant workers, and 10.71 Sv for the plutonium production plant workers. By contrast, radiation doses for workers at US nuclear plants rarely exceeded dose and exposure limits.

During the first year of project 2.2, the choice of a suitable comparison group was evaluated (See appendix 4 of the attached Final Report). Preliminary analyses of Mayak worker data have been based on comparisons with national vital statistics, but the appropriateness of such comparisons is questionable given concerns related to the "healthy worker effect". Also, as noted in appendix 4 of the Final Report, relevant national statistics for the USSR are not available for all disease categories of interest, and specifically are not available for leukemia or for bone and liver cancer, are not available for all calendar year periods, and are limited to broad age categories. Furthermore, because the assignment of cause of death in Mayak workers has often made use of autopsy data and medical records, this information may not be comparable to that used in national statistics.

Work during the first year also explored the use of internal comparisons. However, the Mayak study differs from those conducted in other countries, where the cohorts included large numbers of workers performing non-radiation work with little potential for exposure. For Mayak workers who were initially employed in later periods, this may not be a serious problem as there are many workers with very low doses. However, for the early period, the vast majority of workers had non-trivial doses, making it difficult to conduct reliable internally based dose-response analyses. For example, among reactor workers who began working in 1948-1958, only 551 (of a total of 2413) had never received an annual dose exceeding 50 mGy. Use of workers in the radiochemical and plutonium production plants as controls is probably not reasonable because of the possibility of unmeasured plutonium exposure, since routine plutonium monitoring did not begin until 1970.

Other control groups were also considered. Possibilities are unmonitored workers (not monitored for external radiation) who worked at the main plants and who are currently included in the Mayak Worker Registry, and other workers who worked at auxiliary plants and departments of Mayak (such as the instrument-making plant, the water preparation plant, and the central Mayak laboratory) and who are not currently included in the registry. Concerns regarding these workers are that they may have visited main plants and been exposed without adequate monitoring, and that medical criteria for selection of such workers may not have been as high as for monitored workers at the main plants.

Research Design and Methods

Methods are described for each of the tasks indicated under the "Specific Aims" section of this proposal.

Task 1: Improvement of the computer database. At the present time, the computer database is organized so that workers are assigned to one of three registries according to the plant they worked in: reactors, radio-chemical plant, or plutonium production plant. Subjects who were employed in more than one plant were assigned to the most dangerous plant with the plutonium production plant being considered the most dangerous, and the reactors considered the least dangerous.

Task 1 is aimed at developing a database that includes all workers, and that provides data on which of the three plants workers were employed during any given time period. This information is available but has not been fully computerized. Such information could be particularly important if one wished to develop correction factors for missed neutron dose, as these factors will depend on the location of the worker.

Also, it has been determined that some workers in the registry had worked earlier in departments not included in the registry, but during this early period had visited the main plants and been exposed during these visits. For such workers, information on periods of employment involving exposure needs to be included, even if this employment was not in the three main plants noted above.

In addition to the work noted above, a comprehensive set of logical checks will be performed (for example, checks to insure that hire dates precede termination dates, etc.). These checks will be similar to those used, for example, in developing the Hanford database as described by Gilbert et al. (1992). Discrepancies that are identified will need to be investigated and resolved appropriately.

Task 2: Update of vital status data. Vital status and cause of death information will be updated to extend to the end of 1996. The procedures used to accomplish this are those that have been used in the past, and which are described in appendix 2 of the Final Report on the first year of work. (Attached as an appendix to this proposal.)

Task 3: Development of an adequate control group. As discussed in Sections 3 and 4 of this proposal, there are serious limitations to the use of national statistics as a basis for comparison for Mayak workers. Also, because of the very limited number of workers with low doses in the early period of operations, internal comparisons by level of dose are also unlikely to be adequate if based on monitored workers currently included in the Mayak Worker Registry.

This task will expand the number of workers with either no occupational dose or relatively low occupational doses. These additional workers can then be included in dose-response analyses addressing the effects of both external and internal exposures. As noted in section 3, when conducting dose-response analyses by level of radiation dose, all workers with relatively low exposures provide important comparative information that permits more reliable and precise estimation of risk per unit of exposure, and it is not necessary to specifically designate a "pure" unexposed group.

In preliminary work discussed in section 4, two principal groups were identified for possible use as controls: unmonitored workers who are already included in the Mayak registry but who have not been included in analyses conducted to date; and workers in the auxiliary plants of Mayak including the instrument-making plant, the water preparation plant, the central Mayak laboratory, and other auxilliary departments. A third group, which is less promising, is Ozyorsk workers who did not work at the Mayak plants.

The unmonitored workers have the major advantage that they are already in the registry and vital status information is already available. Concerns are that some of these workers might have visited the main plants on a regular basis and thus received exposure that was not measured, and that some workers may have been exposed to plutonium. Thus, for this group, job history records and other available data will need to be examined to eliminate those who appear to have received substantial radiation doses and those who worked in the plutonium and radiochemical plants.

There is also concern that medical criteria for these workers were not as strict as for workers at the Mayak main plant, and that for this reason their baseline cancer risks might be higher than for other Mayak workers. This can be explored by conducting analyses that compare risks in unmonitored workers with risks in reactor workers with lower doses. Although small numbers may limit such comparisons, strong biases in the direction of higher risks for unmonitored workers could be detected. (Biases in the other direction would be difficult to distinguish from an exposure effect.) Still another approach for evaluating these workers is to conduct dose-response analyses with and without their inclusion. If risk estimates decreased markedly with the inclusion of unmonitored workers, one might suspect bias.

Adding workers in Mayak's auxiliary departments is a more difficult task, and requires reviewing 30-40,000 registration cards from the personnel departments in order to create a control group of about 2-3,000 auxiliary workers. These workers will be selected to be similar with respect to age and sex to Mayak workers initially employed during the period 1948-58. Like the unmonitored workers, it will be necessary to exclude, to the extent possible, workers with unmeasured external dose or with plutonium exposure. Similar analyses to the those proposed for unmonitored workers can be conducted to investigate the comparability of baseline cancer risks for these workers and for other Mayak workers. In addition, unmonitored and auxiliary workers can be compared, and the sensitivity of dose-response analyses results to which low exposure workers are included can be investigated.

A additional possible resource for identifying a comparison group is the Children's Registry. The registry includes 50,000 persons born in Ozyorsk from 1948-88 or who moved to Ozyorsk before age 15 and were resident there for at least one year. Most of these subjects have been traced, and the registry includes information on the employment of the parents at Mayak and information on parental occupational doses. Thus parents who either worked in auxiliary departments at Mayak or who did not work at Mayak might be considered for selection as comparison subjects. This approach will be explored if identifying auxiliary workers through other means proves difficult, or if it is found necessary to expand the control group to include subjects who did not work at Mayak.

Still another approach that will be considered is the use of workers initially employed in later years (with lower doses) as a comparison group for early more highly exposed workers. Because workers tended to be young at their start of employment, such comparisons may not work well unless adjustment for calendar year period is dropped. Trends in national statistics (where available) over time could be examined to determine the appropriateness of this approach, which would be reasonable only for certain types of cancer.

The use of national statistics will not be entirely abandoned, and some analyses making use such statistics will be conducted. Further efforts will be made to explore the availability of additional statistics by writing to appropriate departments in Moscow and other locations.

It is hoped that having a variety of options regarding comparison groups will strengthen this study. If results are found to be insensitive to the choice comparison group, then one is in a much stronger position to draw firm conclusions. If this choice does affect results, it is important that this be known. It is of course important to have an a priori choice of subjects that are to be included in the dose-response analyses that are emphasized in the presentation of results. The analyses given emphasis will very likely be internally based dose-response analyses that include both unmonitored workers and the selected auxiliary plant workers.

Task 4: Conduct dose-response analyses to evaluate risks of lung, liver and bone cancer resulting from plutonium exposure. Under the project currently being funded by the NCI, dose-response analyses based on external doses are being conducted. This proposed project will expand these analyses to include analyses addressing the effects of dose from internally deposited plutonium. Initial analyses will address the risk of lung cancer and will thus be based on estimated doses to the lung, including both external and internal components. Later, analyses of the risks of bone and liver cancer will be conducted. The best available dosimetry data will be used in these analyses, and will make use of any relevant work to improve historical dosimetry.

A difficulty in addressing the effects of plutonium exposure is that routine monitoring of workers for such exposure did not begin until 1970. Thus, workers in the radio-chemical and plutonium production plants who left Ozyorsk or died before this time could have had undetected plutonium exposure. For this reason, it is necessary to exclude experience (person-years) of workers in the two plants prior to their date of first monitoring.

Since most workers with internal doses also have external doses, it is necessary to include both components of dose. Two approaches are proposed.
In the first, the quality factors recommended by the ICRP will be applied to the alpha dose in Gy. Alternative choices may also be evaluated to determine the sensitivity of results to this choice. For these analyses, reactor operators with higher doses would probably be excluded as they would contribute little information regarding plutonium exposure. In the second approach, an attempt will be made to estimate separate coefficients for the internal and external dose components, although it is recognized that separating these effects may be difficult.

Analyses will be conducted using the AMFIT module of the software package EPICURE. Adjustment through stratification will be made for age, calendar year period, sex, and plant. The possible modifying effects of plant and sex will be explored and will be evaluated on both relative and absolute scales. If strong modifying effects are found, emphasis will be put on separate presentation of results by plant and/or sex. For comparison of risks with those from other sources, the excess relative risk model, in which the risk is a linear function of dose, will be the primary model evaluated. Departures from a linear-dose response will be investigated by fitting other functions such as linear-quadratic and power functions.

Both external and internal doses will be treated as time-dependent variables. For the latter, this will require information from dosimetrists on cumulative dose as a function of time. The approach is expected to be similar to that used by Khokhriakov and Romanov (1996) for Mayak workers and by Gilbert (1990) in analyzing the effects of plutonium exposure in dogs. Emphasis will be placed on cumulative dose with a lag of ten years, but other lags and dose metrics will also be explored.

Task 5: Comparison of the results of analyses conducted under task 4 with results from studies in the United States. As noted in Section 3, information on plutonium-related effects from U.S. studies is limited. Nevertheless, after completing the analyses of the Mayak worker data, the current status of studies of U.S. workers involving plutonium exposure will be reviewed. In interpreting the Mayak findings, the U.S. findings will be discussed, and whatever comparisons seem appropriate will be made. Because analyses of U.S. data have generally been based on body burden rather than on dose to various organs, it may be necessary to conduct similar analyses for Mayak workers as a supplement to those based on dose.

Time Schedule. The work to be accomplished in each of three years on each of the five proposed tasks is indicated below. Progress reports will be prepared every six months.

Year 1: Under task 1, both the improvement of the information on plant of employment and the logical edits will be initiated in year 1, and it is anticipated that most of this work will be completed during this year. For task 3, available records for unmonitored workers and those with low doses (< 0.1 Gy) will be examined to eliminate those who appear likely to have received substantial radiation doses. Efforts to develop a control group of workers from Mayak's auxiliary plants will also be initiated.

Year 2: Work on tasks 1 that has not been completed during year 1 will be completed during year 2. Task 2, addressed at updating vital status data will be carried out. Under task 3, work to identify auxiliary plant controls will be continued, and, if necessary, work to identify non-Mayak worker controls will be initiated. Also under task 3, analyses addressing the comparability of baseline risks unmonitored workers, lower dose Mayak workers, and auxiliary workers will be conducted. Under task 4, initial dose-response analyses addressing the risks of lung, bone, and liver cancer resulting from plutonium exposure will be conducted.

Year 3: Work under task 3 to expand the comparison group will be completed. The third year will be primarily devoted to completing dose-response analyses addressing risks of lung, bone, and liver cancer (task 4). A paper will be prepared describing these analyses, and this paper will include discussion of how Mayak results compare with those based on U.S. workers (task 5).

Quality Assurance/Quality Control

Data quality control carried out during the first year of this study will be continued for this long-term project. The completeness of the cohort will be checked to ensure that it includes all persons who initiated employment at the three main plants during the period 1948-72. It is noted that task 1 is specifically addressed at improving the quality of the computer database, and that task 3 includes checking dosimetry data for unmonitored and low dose workers. Also, current work being conducted under the NCI contract is addressed at improving the quality of the cause of death information.

Collaborators/Collaborating Institutions

The principal institution conducting this long-term project in the Russian Federation is Branch N 1 of the State Scientific Center Biophysics Institute (FIB-1). Scientists from the Mayak PA and the State Scientific Center Biophysics Institute will be co-investigators. Control will be carried out by the Executive Committee (from the Federal Department of MBEP MHMI RF - a member of the Executive Committee, deputy chief of the Federal Department M.F.Kisselyov).

The following scientists from FIB-1 will be involved in the work on the assessment of the risk of stochastic effects within the framework of the project:

Principal investigator - N.A.Koshurnikova
Participating Investigators: M.G.Bolotnikova,
V.V.Kreslov,
P.V.Okatenko,
M.E.Sokolnikov,
N.S.Shilnikova.
M.A.Okatenko

The investigator from the State Scientific Center Biophysics Institute is L.A.Buldakov.

The following scientists from FIB-1 will be involved in organizing and carrying out the work on the assessment of internal doses:

Principal investigator - V.F.Khokhryakov
Participating Investigators: K.G.Suslova,
S.A.Romanov,
T.I.Kudryavtzeva
I.A.Orlova

The following scientist from Mayak PA will be involved in the work on dosimetry of external radiation:

Principal investigator - E.K.Vasilenko.

American scientists who will serve as leaders for this project Dr. Ethel Gilbert and Dr. Elaine Ron from the National Cancer Institute

The roles of each of these scientists are briefly described below. Curricula vitae are found in Appendix .

Dr. N.A. Koshurnikova is the principal investigator for this project at FIB-1. She has been associated with the Mayak worker registry since its inception, and has been responsible for the development of follow-up procedures and analyses of the data. In addition to her overall responsibility as principal investigator, she will be responsible for preparing written materials that describe and summarize the work, and for organizing meetings of Russian and American project staff. Dr.Koshurnikova will spend 25% of her time on this project.

Dr. V.V. Kreslov is the head of the epidemiology laboratory at FIB-1, and is responsible for organizing and carrying out work related to data collection, management and analysis. He will coordinate responsibilities among the project staff, and will also contribute to the preparation of reports on the project. Dr.Kreslov will spend 25% of his time on the project.

Dr. M.G. Bolotnikova, Dr. M.E. Sokolnikov, Dr. N.S. Shilnikova, and Dr. L.G. Filippova are research workers at the FIB-1 epidemiology laboratory. They will contribute in the areas of data collection, management and analysis. Their responsibilities include updating vital status information and creating the new control group from workers at the auxiliary departments of the "Mayak" PA and, if necessary, from inhabitants of Ozyorsk who never worked at Mayak. Although the exact details of how the work will be allocated among these scientists will be worked out as the project develops, the areas where individual investigators are likely to focus their attentions are indicated below.

Dr. Bolotnikova will spend 25% of her time on this project. She will be responsible for organizing biophysical examinations of Mayak's workers on plutonium body burden in order to enlarge the cohort of workers in which effects of plutonium exposure can be studied.

Dr. Sokolnikov will check the occupational histories of workers at the radiochemical and plutonium production plants of Mayak who were not monitored for external exposure or whose accumulated dose was below 0.1 Gy in order to create an internal control group. He will spend 100% of his time on the project.

Dr. Shilnikova will be responsible for obtaining the information on deaths that occurred in Ozyorsk in 1995 and verifying causes of death through medical documents (medical histories, autopsy records), and for adding to the database the data on deaths that occurred outside the town in 1993-1995. She will spend 25% of her time on the project.

Dr. L.G.Filippova will be responsible for tracing Mayak worker cohort members and updating the information on vital status. She will spend 100% of her time on the project.

Dr. P.V. Okatenko has extensive experience with personal computers and is responsible for database design and development and for data analysis. He will be responsible for developing computer programs to enter new data (for example, detailed occupational histories), and for analysis of the data using the software package EPICURE (AMFIT). He will spend 25% of his time on the project.

Dr. L.A. Buldakov is Deputy Director of the State Scientific Center "Biophysics Institute", Doctor of Medicine, and Academician of the Academy of Medical Sciences of the Russian Federation. He is an expert in radiation risks, radiobiology and radiotoxicology and will spend 10% of his time on this project. He will be responsible for evaluating the role of these data with respect to their suitability for setting radiation safety standards.

Dr. Ethel Gilbert and Dr. Elaine Ron will work closely with the Russian scientists on this project. They will provide statistical and epidemiologic support, will take an active role in preparing written materials that describe and summarize this work, will assist in training project staff, and will facilitate communication between the Russian project group and foreign scientists. They will visit FIB-1 three times (annually) during the course of this project, and will also meet with FIB-1 scientists at relevant conferences and other occasions when they are visiting the United States. They will remain in close communication with FIB-1 scientists between these visits.

Human Subjects Considerations

Access to identifying personal information of subjects is limited to investigators at FIB-1 and such information will not be made available outside this institution. Investigators at FIB-1 understand the need for confidentiality of this information, and information that might reveal the identity of any subject in the studies will not be included in materials, including publications, that are circulated outside FIB-1. The study is based entirely on paper and computerized records, and does not require personal contact with subjects. An Institutional Review Board (IRB) was set up for the NCI contract, and this committee will also review the proposed study.

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Budget Request for project 2.2.

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Institution: Branch No 1 of the State Scientific Center "Biophysics Institute"

Complete Address: Ozyorskoye shosse, 19 Ozyorsk, Chelyabinsk region, 456780 Russia

Name of Principal Investigator: Nina A.Koshurnikova

Telephone: (35171)76627 **Fax:** (35171)22374

Name of Contact Person: Eduard R.Lyubchansky

Telephone: (35171)75464 **Fax:** (35171)22374

Requested items

Requested items	**1st year**	**2nd year**	**3rd year**	**Total**
A.Equipment (see attached sheet for details)	**6,920**	**6,920**	**-**	**13,840**
B.Supplies (see attached sheet for details)	**1,060**	**1,060**	**1,060**	**3,180**
C.Estimated Travel Costs				
International	18,000	18,000	24,000	60,500
Domestic	2,000	2,000	2,920	6,920
Travels of American collaborators to Russia	10,000	10,000	10,000	30,000
Subtotal	**30,000**	**30,000**	**36,920**	**96,920**
D.Personnel and Other Costs				
D.i) Project Personnel Costs				
Scientists	12,000	12,000	12,000	36,000
Laboratory assistants	4,000	4,000	4,000	12,000
Technical personnel (support)	2,000	2,000	2,000	6,000
Subtotal	**18,000**	**18,000**	**18,000**	**54,000**
D ii)Indirect and/or Other Costs				
Address bureaus information and death certificate access	5,000	5,000	5,000	15,000
Telecommunication	500	500	500	1,500
Fringe benefit cost (40.5% of Direct Labor Cost)	7,290	7,290	7,290	21,870
Overhead including value-added tax	16,230	16,230	16,230	48,690
Subtotal	**29,020**	**29,020**	**29,020**	**87,060**
Total Costs	**85,000**	**85,000**	**85,000**	**255,000**

Equipment and supplies

Items	Unit	U.S.$$ Per unit	U.S.$$ Per item
A.Equipment			
Computer Packard Bell 540 D	2	2,300	4,600
Packard Bell SVGA color monitor	1	830	830
CTX SVGA color monitor	1	930	930
Strimmer Archive XL9250 ext	1	572	572
Net adapter EtherExpress 16 Flash-c	6	140	840
Systipak cabling kit	1	614	614
CD-ROM 4-speed, IDE	1	185	185
Back-UPS Pro 420	2	250	500
Microsoft natural keyboard	2	125	250
Printer HP Laser Jet 5P	1	1,190	1,190
Printer HP Laser Jet 850C	1	730	730
Microsoft Windows-95	1	152	152
Microsoft Office for W-95	1	305	305
Borland Delphi Client-Server	1	1,591	1,591
Norton Utilities for W-95	1	139	139
Microsoft Visual FoxPro professional ed.	1	413	413
	Subtotal		**13,841**
When available, Russian localised versions of software and hardware assumed			
B. Supplies			
Epson LX-1050 ribbon cartridge	10	6	60
Diskette Verbatim teflon	100	1.5	150
ZOOM paper, A4, 500 sh.	30	6	180
A3 paper, 500 sh	4	10	40
OverHead slides	2	80	160
Color ink cartridge HP DJ850C	4	35	140
Toner cartridge HPLJ5P	2	165	330
	Subtotal		**1,060**

Equipment purchase and supplies justification

Computer hardware and software will be used to maintain the worker registry. The necessity to ensure data safety demands to use Back-UPS as well as tape drives. Printers should be purchased to quickly print documents (papers, reports etc.) of good quality. Purchased equipment and the equipment already available in the laboratory (used for this project) will be provided with the supplies listed above.